Pharmacologic Management of Alcohol Use Disorders in the Primary Care Setting

Sanjay Paidisetty, BS, and Adam J. Gordon, MD, MPH

Abstract

- **Objective:** To examine the rationale and evidence to support pharmacotherapies to treat alcohol problems in the primary care setting.
- **Methods:** Qualitative review of the literature.
- **Results:** Problem alcohol consumption is a prevalent problem in the United States and results in significant morbidity and mortality. In recent years, new pharmacologic treatments have been approved by the U.S. Food and Drug Administration to help healthcare providers treat patients with alcohol problems. The available research has shown that disulfiram, naltrexone, and acamprosate are effective for treating patients with alcohol problems. Certain patient characteristics promote enhanced outcomes for each medication. Whether combinations of pharmacotherapies or combinations of pharmacotherapy with nonpharmacotherapy enhance outcomes for problem drinkers are active research topics.
- **Conclusion:** Primary care providers should strongly consider the use of pharmacologic treatment as an adjunct to nonpharmacologic therapy to help patients reduce or eliminate alcohol consumption.

An estimated 18 million adults in the United States meet diagnostic criteria for alcohol abuse or alcohol dependence, and many more persons drink alcohol in amounts that place them at risk for alcohol-related harm [1]. The National Institutes of Health defines at-risk or hazardous drinking as consuming more than 14 standard drinks per week (men) or more than 7 drinks per week (women and persons > 65 years) [2]. While estimates vary, as many as 20% of outpatients presenting to primary care are hazardous drinkers [3–5]. Hazardous drinkers and those with alcohol abuse or alcohol dependence (alcohol use disorders [AUDs]) collectively experience the consequences of “problem drinking.”

The medical, social, and societal consequences of problem drinking are not insignificant. Problem drinking increases the risk for other medical complications such as certain cancers, neuropsychiatric diseases, cardiovascular diseases, and gastrointestinal diseases [6]. Furthermore, problem drinking reduces patients’ adherence to medical and psychiatric treatments and may narrow the potential treatment of other illnesses (e.g., hepatitis) [7]. In the United States, the estimated annual economic burden of alcohol problems exceeds $100 billion [8].

Based on the consequences of problem drinking, several authorities have advocated that physicians, especially primary care physicians, play a greater role in screening and treating patients with problem drinking. For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) encourages all primary care and mental health clinicians to incorporate AUD screening, brief intervention, and treatment referral into their practices [2]. The Institute of Medicine, U.S. Preventive Services Task Force, and Centers for Disease Control and Prevention have made similar recommendations [9,10]. To assist busy clinicians in screening for and treating problem drinking, the NIAAA recently published a 30-page monograph, “Helping patients who drink too much: a clinician’s guide,” which provides screening, assessment, and brief intervention support materials (downloadable at http://pubs.niaaa.nih.gov/publications/practitioner/cliniciansguide2005/guide.pdf) [2].

While nonpharmacologic treatment has been the mainstay of treatment for problem drinking, recent scientific advances have encouraged the use of pharmacologic treatments. Pharmacologic treatments for problem drinking can serve as an effective adjunct to nonpharmacologic treatments to help patients reduce or eliminate alcohol consumption. The advance in the understanding of the neurobiology of alcohol dependence and success of pharmacotherapy in other addictions has supported the use of pharmacotherapy to help in the treatment of problem drinking [11]. Unfortunately, pharmacologic treatments have not been widely used [12]. The lack of awareness among clinicians that effective pharmacotherapy options exist is a primary reason for low utilization of pharmacotherapy in clinical practice [13].

The purpose of this review is to examine the rationale and evidence to support pharmacotherapies to treat alcohol
Table 1. Medications Approved for Alcohol Dependence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Adverse Events</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disulfiram (Antabuse)</td>
<td>Odyssey Pharmaceuticals, East Hanover, NJ</td>
<td>Aldehyde dehydrogenase inhibitor</td>
<td>Optic neuritis, peripheral neuritis, polyneuritis, peripheral neuropathy, hepatitis, skin eruptions, headache, drowsiness, psychoses</td>
<td>250-mg tablets for oral administration. Initial: 500 mg/day in a single dose for 1–2 weeks; average maintenance dose: 250 mg daily (range, 125–500 mg). 500 mg is maximum daily dose. Continue administration until patient establishes self-control</td>
</tr>
<tr>
<td>Naltrexone (Depade, ReVia)</td>
<td>Mallinckrodt, Hazelwood, MO, and DuPont Merck Pharmaceutical Co., Wilmington, DE</td>
<td>Opioid receptor antagonist that may block the effects of endogenous opioids</td>
<td>Nausea, headache, nervousness</td>
<td>50-mg scored tablets for oral administration. Initiation: 25 mg. If no withdrawal signs after 1 hour, administer second 25-mg dose; maintenance: 50 mg/day (flexible)</td>
</tr>
<tr>
<td>Naltrexone depot (Vivitrol)</td>
<td>Alkermes, Cambridge, MA</td>
<td>Opioid receptor antagonist that may block the effects of endogenous opioids</td>
<td>Eosinophilic pneumonia, interstitial pneumonia, pain at injection site, nausea, abdominal pain, somnolence</td>
<td>380 mg (in 4 mL diluent vial) by intramuscular injection. Administer every 4 weeks, alternating buttocks</td>
</tr>
<tr>
<td>Acamprosate (Campral)</td>
<td>Forest Pharmaceuticals, St. Louis, MO</td>
<td>May restore to normal the altered balance of neuronal excitation and inhibition induced by chronic alcohol exposure through possible interaction with GABA and glutamate neurotransmitter systems</td>
<td>Diarrhea, nausea, somnolence</td>
<td>333-mg enteric-coated tablet for oral administration. Adults: 666 mg 3 times daily. In moderate renal impairment (creatinine clearance 30–50 mL/min): 333 mg 3 times daily</td>
</tr>
</tbody>
</table>

problems in the primary care setting. The review focuses on the 4 medications approved by the U.S. Food and Drug Administration (FDA) to treat problem drinking: disulfiram (Antabuse), naltrexone (ReVia, Depade), naltrexone depot (Vivitrol), and acamprosate (Campral) (Table 1). In addition to discussing the relevant literature regarding each medication, we also will discuss the suggested neurobiology behind alcohol dependence and factors for selecting a specific pharmacotherapy based on patient characteristics.

**Neurobiology of Alcohol Dependence**

Neurobiologic models of craving may explain why adults consume alcohol in problem amounts [14,15]. These models posit that the cause of excessive consumption and eventual alcohol dependence is through the positive and negative reinforcement effects of alcohol and the behaviors associated with alcohol consumption. It appears that the dysregulation of the dopaminergic/opioidergic pathway and the γ-aminobutyric acid (GABA)/glutamnergic pathways are involved in causing positive reinforcement or reward-seeking behaviors and negative reinforcement or relief-seeking behaviors [16,17].

**Dysregulation of the Dopaminergic/Opioidergic Pathway**

Animal studies suggest that alcohol consumption affects the activity of the mesolimbic pathway, which mediates feelings of reward, such as pleasure and enhanced arousal levels. Alcohol activates dopaminergic connections that project from the ventral tegmental area to the nucleus accumbens, amygdala, bed nucleus of stria terminalis, lateral septal area, and lateral hypothalamus [18]. In the brain, dopamine generally functions to regulate motivation, reinforcement, and fine motor control. Anticipation of or the act of consuming alcohol causes endogenous opioid peptide systems to increase dopamine release [17,19]. One possible hypothesis that explains why alcohol problems can occur is that when a patient consumes alcohol, an increase in dopamine levels induces a pleasurable effect (positive reward). In this scenario, the alcohol drinker consumes alcohol for pleasure, thereby exhibiting reward-seeking behavior [20]. Alcohol can be consumed in higher amounts for its pleasurable effects, and eventually, with increased consumption, alcohol problems can occur. Although dopamine is strongly implicated in positive reinforcement, other animal studies suggest that GABA, opioids, glutamate, and serotonin receptor systems, which process sensory pleasure, also are affected by alcohol consumption and may also be involved in this positive, reward-seeking behavior [21].

**Dysregulation of the GABA/Glutamate Receptor System**

GABA serves as a primary inhibitory neurotransmitter of the brain. Conversely, glutamate serves as a primary excitatory
neurotransmitter of the brain. With chronic alcohol consumption, secondary changes occur in the GABA and glutamate neurotransmission and receptor system. Animal studies suggest that alcohol amplifies the inhibitory activity of GABA and decreases the excitatory activity of glutamate by antagonizing N-methyl-D-aspartic acid (NMDA) receptors. Furthermore, chronic alcohol consumption down-regulates the effect of GABA and up-regulates the effect of NMDA. This can lead to a person’s tolerance to the effects of alcohol. Tolerance, in turn, leads to increased consumption and further NMDA up-regulation. When alcohol is acutely removed from the system after chronic intake, the unopposed, up-regulated NMDA/glutamate system exhibits hyperexcitability that is associated with alcohol withdrawal syndrome [22,23]. Through these mechanisms, the negative reinforcement of a patient to avoid the negative effects of reduced alcohol consumption, including alcohol withdrawal syndrome, increases the difficulty of a patient to reduce or abstain alcohol consumption [24].

Neurobiologic evidence suggests both positive and negative reinforcement pathways mediate alcohol craving. The differential action of the positive and negative reinforcement pathways supports the use of different medications for different phenotypes of alcohol-dependent patients: those who use alcohol primarily for positive effects (e.g., pleasure) and those who use alcohol primarily to avoid negative consequences (e.g., alcohol withdrawal syndrome). Despite these distinctions in problem alcohol drinkers, identifying the underlying cause of a patient’s addiction is challenging, and patients may not fit into this dichotomous phenotypic classification. FDA-approved medications for problem alcohol drinking interact with both the positive (e.g., naltrexone) and negative (e.g., acamprosate) pathways and may support the combined effect of dual medications to treat problem alcohol consumption.

### Medications for Treating Alcohol Dependence

The primary goal of treatment of problem drinking may be abstinence or may be reduction in alcohol consumption (e.g., harm reduction). Studies of pharmacotherapy in problem alcohol drinking use a variety of outcome measures, including abstinence/relapse rate, time to first drink, time to heavy drinking, cumulative abstinence days, and drinks per drinking day (Table 2). When considering pharmacotherapy, practitioners and patients should mutually decide what the goals of alcohol treatment for problem drinking will be. In addition, in deciding on which pharmacotherapy to use, it may be useful to consider if there is evidence that the medication is associated with achievement of the desired treatment outcome as well as to monitor for changes in patient outcome goals.

### Disulfiram

Disulfiram (Antabuse) was approved by the FDA in 1948. It is indicated to aid in the management of certain chronic alcohol-consuming patients who desire to remain in a state of enforced sobriety so that psychotherapeutic therapy will have the most beneficial effect [25]. The action of disulfiram is to deter a patient from initiating alcohol consumption after abstinence. The mechanism for this effect is due to an inhibition of the enzyme acetaldehyde dehydrogenase. After consumption of alcohol, ethanol is initially metabolized by alcohol dehydrogenase to produce acetaldehyde, which is then metabolized by acetaldehyde dehydrogenase to produce acetate. Disulfiram irreversibly inhibits the acetaldehyde dehydrogenase enzyme to lead to an accumulation of the acetaldehyde. The increased serum acetaldehyde level with the consumption of alcohol in a patient on disulfiram causes intense nausea, flushing, and emesis. The result of these actions is that disulfiram is used as a psychological deterrent: consuming alcohol in a disulfiram-treated patient will make the patient sick. A patient well informed about the effect of a disulfiram will avoid consuming alcohol to avoid the toxic effects of increased levels of acetaldehyde due to alcohol consumption [11].

Controlled trials testing disulfiram’s efficacy are limited and difficult to conduct due to the necessity of both the patient and physician knowing which treatment is being used, ease of a patient to discontinue treatment under unsupervised conditions, and the difficulty in determining if the biologic or psychological effect is responsible for efficacy [11,26]. In the study by Fuller et al, the largest and most methodologically controlled trial to date, 600 male alcoholic veterans were randomized into 3 treatments over a course of 1 year [27]. Subjects were randomized to 1 mg disulfiram (effectively, an inactive disulfiram), 250 mg disulfiram (active), and placebo. Since patients were educated about the disulfiram-ethanol reaction prior to treatment initiation, the 1-mg dosage tested the efficacy of disulfiram as a psychological deterrent to

---

Table 2: Definitions of Common Outcome Measures

<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence rate</td>
<td>% of patients that remained abstinent throughout study</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>% of patients that relapsed into drinking (or heavy drinking)</td>
</tr>
<tr>
<td>Cumulative abstinence duration</td>
<td>Sum of all abstinent days throughout a trial</td>
</tr>
<tr>
<td>Percent days abstinent</td>
<td>% of cumulative abstinence duration over study period</td>
</tr>
<tr>
<td>Time to heavy drinking</td>
<td>Relapse involving ≥ 5 drinks/day for men and ≥ 4 drinks/day for women: a standard drink = 10 g alcohol</td>
</tr>
<tr>
<td>Time to first drink</td>
<td>Length of time to a relapse to any drinking</td>
</tr>
</tbody>
</table>
drinking. No significant differences were found between the groups in abstinence rates and time to first relapse. However, among patients who relapsed, those on the 250-mg dosage had significantly fewer drinking days compared with the other 2 groups. Among the 20% of patients who were compliant throughout the study, 43% remained abstinent through treatment, significantly greater than the 8% of noncompliant patients who remained abstinent. The study demonstrated disulfiram’s limited efficacy under unsupervised conditions and that poor compliance produces limited disulfiram results. Disulfiram, therefore, is perhaps best indicated for patients who are having difficulty attaining sobriety, who are motivated to obtain complete abstinence, who are compliant with treatment, or can be treated in supervised settings ([26,28]). Disulfiram implants have not been shown to be effective in producing better results than placebo and may lead to additional adverse events [29–31]. Disulfiram implants are not approved for use in the United States.

If prescribed, patients should be abstinent from alcohol. Patients are typically started on a dose of 500 mg daily. Full effect occurs within 12 hours, and the potential for ethanol interaction can last up to 14 days. For maintenance, the dose can be reduced to 250 mg. Multiple cases of hepatitis have been reported with administration of disulfiram. Other common side effects include neuritis and skin eruptions. Disulfiram is contraindicated in patients receiving metronidazole, with severe myocardial disease or coronary occlusion, or with psychoses. More severe ethanol-disulfiram reactions include myocardial infarction, congestive heart failure, respiratory depression, and death. Patients must be reminded to avoid any medications or foods that may contain ethanol or aldehyde, such as certain antitussive formulations, sauces, and vinegar.

In the primary care setting, disulfiram has not traditionally been used as a treatment for alcohol dependence due to lack of strong evidence for efficacy in this setting, the side effect profile, and the need to closely monitor patients for adherence to the medication [32,33]. Furthermore, its action of aversion to alcohol and negative message (ie, “If you drink this, you will get sick”) is contrary to the action of motivation and positive message of nonpharmacologic treatment (ie, “If you cut down drinking, you will get better”), as practiced in typical brief interventions. Several research studies have examined disulfiram as an adjunct to nonpharmacologic and other pharmacologic therapies for alcohol consumption with mixed results (see discussion below). Disulfiram may have primary utility for patients who need to or desire to be completely abstinent, such as alcohol-dependent professionals or patients in the criminal justice system.

Acamprosate
Calcium acetylhomotaurinate, acamprosate (Campral), is a structural analogue of GABA [34]. It was approved by the FDA in 2004 to maintain alcohol abstinence among alcohol-dependent patients who are abstinent at treatment initiation [35]. As of this writing, the exact mechanism of action of acamprosate is unknown, but animal studies suggest acamprosate may act by normalizing NMDA receptor and glutamergic hyperactivity seen in continued alcohol consumption and alcohol withdrawal syndrome [36]. It is uncertain if acamprosate’s proposed attenuating effects on NMDA receptors are direct or indirect. The attenuating effects are believed to result in reducing physiologic distress of withdrawal and reduce the desire for alcohol during periods of abstinence [34,37].

Acamprosate’s clinical efficacy is mixed in published controlled clinical trials (Table 3). Many of the earlier acamprosate studies, conducted in Europe, show acamprosate to have beneficial effects over placebo in alcohol-dependent patients using total abstinence and cumulative abstinence duration as primary outcomes [36,38]. Evidence also suggests that acamprosate may aid patients in regaining abstinence if they relapse during treatment [22]. Several other studies do not support the use of acamprosate [39–41].

Recent large U.S. studies failed to show as positive results for using acamprosate for certain subsets of patients with problem alcohol consumption. For example, Mason et al studied 601 alcohol-dependent patients desiring consumption reduction or abstinence who were randomly assigned to receive either 2 g acamprosate, 3 g acamprosate, or placebo. Investigators compared intention-to-treat patients (all randomized patients with any outcome data) with patients motivated towards abstinence. In the intention-to-treat group, the benefit of acamprosate over placebo was seen only in improving abstinence rates. However, examination of patients motivated towards abstinence demonstrated a positive effect of acamprosate versus placebo in abstinence rates, number of drinks per week, and number of days per week. Mason’s results suggest acamprosate may not be effective in nonabstinent and nonmotivated patients [42]. In the recently published COMBINE study (described in more detail later), there were no differences between acamprosate and placebo in increasing percent days abstinent or decreasing time to first heavy drinking day during the treatment period and for up to 1-year follow-up [43]. The differences in outcomes of various acamprosate studies may be due to varied sample characteristics and settings of inclusion (eg, inpatient versus outpatient settings, pretreatment abstinence requirements) and further work is needed to examine subgroups of patients that may preferentially benefit from this medication.

Acamprosate is administered in a 333-mg enteric-coated delayed-response tablet. The recommended dosage is two 333-mg tablets 3 times daily. Serum steady state is attained after 5 days. Treatment should be initiated during abstinence, and since acamprosate has no alcohol interaction, it should be maintained through relapses [22,44]. Nausea,
### Table 3. Acamprosate Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration</th>
<th>Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balteri 2003 [107]</td>
<td>2-arm study ACP vs P</td>
<td>R DB PC</td>
<td>ADI OP</td>
<td>12 w T 12 w PTFU</td>
<td>BOSC AA</td>
<td>Abs AE</td>
<td>“...safe and effective in treating alcohol-dependent patients and to maintain the abstinence during 24 weeks.”</td>
</tr>
<tr>
<td>Chick 2000 [39]</td>
<td>2-arm study ACP vs P</td>
<td>MC R PC</td>
<td>AIT AD</td>
<td>6 m T 1 m PTFU</td>
<td>PT</td>
<td>Abs</td>
<td>“...no evidence of an effect of acamprosate on drinking in the 6 months following detoxification was found.”</td>
</tr>
<tr>
<td>COMBINE 2006 [43]</td>
<td>9-arm study ACP vs NTX vs ACP+NTX vs P vs CBI only</td>
<td>MC R DB PC</td>
<td>AIT AD</td>
<td>4 m T 12 m PTFU</td>
<td>CBI MM</td>
<td>AE Comp Cons Cra D Labs</td>
<td>“...acamprosate showed no evidence of efficacy, with or without CBI.”</td>
</tr>
<tr>
<td>Geerlings 1997 [108]</td>
<td>2-arm study ACP vs P</td>
<td>MC R DB PC</td>
<td>AIT AD</td>
<td>6 m T 6 m PTFU</td>
<td>PT</td>
<td>Abs</td>
<td>“...therapeutic advantage of the acamprosate-treated patients was still present 6 months after treatment...It is concluded that acamprosate could be a useful adjuvant to psychosocial treatment.”</td>
</tr>
<tr>
<td>Gual 2001 [109]</td>
<td>2-arm study ACP vs P</td>
<td>MC R DB PC</td>
<td>AD OP</td>
<td>6 m</td>
<td>PT</td>
<td>Abs</td>
<td>“...our results show that acamprosate can be used from the beginning of the withdrawal phase without any unfavorable interaction with acute withdrawal medication.”</td>
</tr>
<tr>
<td>Kiritze-Topor 2004 [110]</td>
<td>2-arm study ACP + SC vs SC</td>
<td>R OL</td>
<td>AD OP</td>
<td>12 m</td>
<td>SC</td>
<td>AE Con PA</td>
<td>“Adjunctive therapy with acamprosate in primary care is associated with significantly better functional outcome.”</td>
</tr>
<tr>
<td>Lhuintre 1990 [111]</td>
<td>2-arm study ACP vs P</td>
<td>MC R DB PC</td>
<td>IP</td>
<td>3 m</td>
<td>PT</td>
<td>AE Labs Comp</td>
<td>“...proved superior to placebo on the evolution of markers of alcohol ingestion at three months, in this large-scale multicenter study.”</td>
</tr>
<tr>
<td>Namkoong 2003 [40]</td>
<td>3-arm study ACP-LD vs ACP-HD vs P</td>
<td>MC R DB PC</td>
<td>AD OP</td>
<td>6 m</td>
<td>BC</td>
<td>AE Cons</td>
<td>“...safe and well tolerated in a broadly inclusive sample of alcoholics and appears effective in populations of patients motivated to have a treatment goal of abstinence.”</td>
</tr>
<tr>
<td>Paillet 1995 [112]</td>
<td>3-arm study ACP-LD vs ACP-HD vs P</td>
<td>MC R DB PC</td>
<td>AIT AD</td>
<td>12 m T 6 m PTFU</td>
<td>PT</td>
<td>Abs</td>
<td>“As an adjunct to psychotherapy, this study supports the inclusion of acamprosate in a strategy for treating alcoholism.”</td>
</tr>
<tr>
<td>Pelc 1997 [113]</td>
<td>3-arm study ACP-LD vs ACP-HD vs P</td>
<td>MC R DB PC</td>
<td>AIT AD</td>
<td>3 ms</td>
<td>C SS</td>
<td>Abs AE Cra D Labs PA THD</td>
<td>“For all efficacy parameters, acamprosate appeared to be significantly superior to placebo, with a trend towards a better effect at the higher dosage.”</td>
</tr>
</tbody>
</table>
Table 3. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration</th>
<th>Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poldrugo</td>
<td>2-arm study ACP vs P</td>
<td>MC</td>
<td>AIT</td>
<td>6 m T</td>
<td>RT</td>
<td>Abs, AE, Cons, Labs, THD</td>
<td>“...may be a useful pharmacological compound for the long-term treatment of alcohol-dependence when applied in a community-based rehabilitation programme.”</td>
</tr>
<tr>
<td>Roussaux</td>
<td>2-arm study ACP vs P</td>
<td>R</td>
<td>AD</td>
<td>3 m</td>
<td>C</td>
<td>Abs, Comp, Cra, Labs</td>
<td>“It appeared no significant differences between the 2 groups of patients.”</td>
</tr>
<tr>
<td>Sass</td>
<td>2-arm study ACP vs P</td>
<td>MC</td>
<td>AD</td>
<td>48 w T</td>
<td>C</td>
<td>Abs, AE, Cons, Labs, THD</td>
<td>“...proved to be a safe and effective aid in treating alcohol-dependent patients and in maintaining the abstinence of patients during 2 years.”</td>
</tr>
<tr>
<td>Tempesta</td>
<td>2-arm study ACP vs P</td>
<td>MC</td>
<td>AD</td>
<td>6 m T</td>
<td>C</td>
<td>Abs, AE, Comp, Cons, Cra, D, PA, THD</td>
<td>“Patients on acamprosate had a higher continuous abstinence rate and experienced less severe relapses...Treatment remained positive, but not significant, 3 months after termination of study medication.”</td>
</tr>
<tr>
<td>Whitworth</td>
<td>2-arm study ACP vs P</td>
<td>MC</td>
<td>AD</td>
<td>12 m T</td>
<td>C</td>
<td>Abs, AE, Cons, Labs</td>
<td>“...an effective and well-tolerated pharmacological adjunct to psychosocial and behavioural treatment programmes for treatment of alcohol-dependent patients.”</td>
</tr>
</tbody>
</table>

AA = Alcoholics Anonymous or other 12-step program; Abs = abstinence, % abstinent, abstinence rate, % slip into drinking, relapse, % relapse, and/or relapse rate; ACP = acamprosate; ACP-HD = high-dose acamprosate; ACP-LD = low-dose acamprosate; AD = alcohol dependent according to DSM criteria; ADI = alcohol dependent according to ICD-10 criteria; AE = adverse events and/or safety measures; AIT = abstinence at initiation of treatment; BC = brief counseling; BOSC = behavior orientation or behavior-oriented supportive counseling; C = counseling; CBI, CBT = cognitive behavioral therapy; Comp = compliance, % study completion; Cons = % days abstinent, amount of alcohol consumption, days between last drink and treatment end, drinking days, drinks per drinking day, days after last relapse, heavy drinking days, pattern of alcohol use, and/or total # of drinks; Cra = craving, urge to drink, and/or alcohol related cues; D = depression and/or anxiety; DB = double-blind; IP = inpatient; MC = multicenter; MM = medical management; NTX = naltrexone; * = optional; OL = open-label; OP = outpatient; P = placebo; PA = patient assessment, addiction severity index [134] and/or alcohol-related problems questionnaire [135] and/or brief psychiatric rating scale [136] and/or clinical global impression [137] and/or 90-item symptom checklist [138] and/or SF-36 [139]; PC = placebo-controlled; PT = psychotherapy, psychoeducation, psychosocial therapy or psychosocial support; PTFU = posttreatment follow-up; PTRP = posttreatment recovery phase (administration of placebo to all groups); R = randomized; RT = rehabilitation treatment program; SC = standard care; SS = social support; ST = supportive therapy; T = treatment; T1 = initial treatment; T2 = following treatment; TFD = time to first drink; THD = time to heavy drinking or time to relapse.

Diarrhea, and somnolence are the most common side effects [43,45]. Unlike other approved pharmacotherapies, acamprosate can be used in patients with liver injury, a common morbidity of patients with significant alcohol consumption. However, acamprosate is contraindicated for patients with severe renal insufficiency as it is excreted unchanged in the urine; therefore, it is recommended not to be used in patients with a creatinine clearance of less than 30 mL/min. Patients with moderate renal insufficiency should receive an initial dose of one 333-mg tablet 3 times daily. Acamprosate can be used with naltrexone, disulfiram, antidepressants, anxiolytics, and hypnotics without serious complications [22].

Naltrexone
Naltrexone (Depade, ReVia) was approved by the FDA in 1994. It is an opioid receptor antagonist indicated for the treatment of alcohol dependence [46]. Similarly to acamprosate, the mechanism for naltrexone is not well understood; however, it is suggested that naltrexone antagonizes the μ-type and possibly δ-type opioid receptors that enhance the release of dopamine in the nucleus accumbens and facilitate reward during alcohol consumption [47]. Naltrexone may prevent “slips” or relapses into alcohol use while in abstinence [14,48].

Similarly to acamprosate, studies of naltrexone’s clinical efficacy versus placebo treatment are both positive and
### Table 4. Naltrexone Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration</th>
<th>Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton 1999 [52]</td>
<td>2-arm study NTX vs P</td>
<td>R DB PC</td>
<td>AIT AD OP</td>
<td>12 w</td>
<td>CBT</td>
<td>Abs AE Cons Cra Labs TFD THD</td>
<td>“…the therapeutic effects of cognitive behavioral therapy and naltrexone may be synergistic” and “…for a number of alcoholic subjects, continued treatment with naltrexone, or perhaps psychosocial intervention, for longer than 3 months is indicated.”</td>
</tr>
<tr>
<td>Anton 2001 [118]</td>
<td>4-arm study NTX vs P</td>
<td>R PC</td>
<td>AD OP</td>
<td>12 w</td>
<td>CBT ST</td>
<td>Abs Comp Cons Cra Labs TFD THD</td>
<td>“Despite being more efficient to administer, the combination of motivational enhancement therapy is less effective than CBT and naltrexone.”</td>
</tr>
<tr>
<td>Balldin 2003 [84]</td>
<td>4-arm study NTX vs P</td>
<td>MC R DB PC</td>
<td>AD OP</td>
<td>6 m</td>
<td>CBT ST</td>
<td>Abs AE Cons Cra Labs TFD THD</td>
<td>“…supports the effect of naltrexone in outpatient treatment of alcohol dependence and suggests that a beneficial interaction effect with CBT can be expected.”</td>
</tr>
<tr>
<td>Chick 2000 [53]</td>
<td>2-arm study NTX vs P</td>
<td>MC R DB PC</td>
<td>AAb AD OP</td>
<td>12 w</td>
<td>PT</td>
<td>Abs AE Cons Cra Labs PA TFD THD</td>
<td>“Naltrexone is effective in treating alcohol dependence/abuse in conjunction with psychosocial therapy, in patients who comply with treatment.”</td>
</tr>
<tr>
<td>COMBINE 2006 [43]</td>
<td>9-arm study ACP vs NTX vs ACP+NTX vs P vs CBI only</td>
<td>MC R DB PC</td>
<td>AIT AD OP</td>
<td>4 m T 12 m PTFU</td>
<td>CBI MM</td>
<td>AE Comp Cons Cra Labs PA TFD THD</td>
<td>“…our data suggest naltrexone can be effective within the context of medical management without specialist behavioral treatment.”</td>
</tr>
<tr>
<td>Croop 1997 [57]</td>
<td>2-arm study NTX vs no meds</td>
<td>MC OL</td>
<td>AIT IP OP</td>
<td>12 w</td>
<td>PT</td>
<td>AE CM Labs</td>
<td>“This is the largest study to date describing the safety of naltrexone in a heterogeneous population of persons with alcoholism. No new safety concerns were identified.”</td>
</tr>
<tr>
<td>Gastpar 2002 [119]</td>
<td>2-arm study NTX vs P</td>
<td>MC R DB PC</td>
<td>AAb AD OP</td>
<td>12 w</td>
<td>RT</td>
<td>Abs AE Comp Cons Cra Labs TFD</td>
<td>“Based upon an intention-to-treat population, this study confirms the safety but not the efficacy of naltrexone in prevention of alcohol relapse.”</td>
</tr>
<tr>
<td>Guardia 2002 [120]</td>
<td>2-arm study NTX vs P</td>
<td>MC R DB PC</td>
<td>AD OP</td>
<td>12 w</td>
<td>RT</td>
<td>Abs AE Comp Cons Cra Labs TFD THD</td>
<td>“…seemed to reduce relapse rate to heavy drinking, but we found no differences in other alcohol consumption variables between naltrexone- and placebo-treated groups.”</td>
</tr>
<tr>
<td>Heinala 2001 [85]</td>
<td>4-arm study NTX vs P then targeted NTX vs P</td>
<td>R DB PC</td>
<td>AD OP</td>
<td>12 w then 20 w</td>
<td>CTS ST</td>
<td>Abs AE</td>
<td>“…confirm the original finding of the efficacy of naltrexone in conjunction with coping skills therapy.”</td>
</tr>
</tbody>
</table>
Table 4. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration</th>
<th>Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hersh</td>
<td>2-arm study</td>
<td>NTX vs P</td>
<td>R DB PC</td>
<td>AD AAb</td>
<td>8 w</td>
<td>RPP</td>
<td>“...individuals with both alcohol and cocaine use disorders are distinct from those depend-</td>
</tr>
<tr>
<td>1998</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ent on alcohol alone, and that NTX at a dosage of 50 mg/day is not efficacious in this pati-</td>
</tr>
<tr>
<td>[121]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ent population.”</td>
</tr>
<tr>
<td>Knox</td>
<td>3-arm study</td>
<td>NTX vs P</td>
<td>R DB PC</td>
<td>AD AAb AD</td>
<td>12 w</td>
<td>UT</td>
<td>AE Comp Cons Cra Labs TFD THD</td>
</tr>
<tr>
<td>1999</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...naltrexone may offer particular benefit to patients who continue to drink during the</td>
</tr>
<tr>
<td>[123]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>early stages of the trial as compared with those who have achieved abstinence before</td>
</tr>
<tr>
<td>Kranzler</td>
<td>3-arm study</td>
<td>NTX vs NFZ</td>
<td>R DB PC</td>
<td>AIT AD</td>
<td>12 w</td>
<td>RPP</td>
<td>AE Comp Cons Cra</td>
</tr>
<tr>
<td>2000</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...associated with significantly more adverse neuropsychiatric and gastrointestinal ef-</td>
</tr>
<tr>
<td>[124]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>fects, poorer compliance, and a greater rate of treatment attrition.”</td>
</tr>
<tr>
<td>Kranzler</td>
<td>4-arm study</td>
<td>NTX vs targeted P</td>
<td>R DB PC</td>
<td>PD OP</td>
<td>8 w</td>
<td>CS</td>
<td>Comp Cons Cra QA REC</td>
</tr>
<tr>
<td>2004</td>
<td>NTX vs targeted P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...attenuated the positive association between heavy drinking and both positive and nega-</td>
</tr>
<tr>
<td>[125]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tive mood, and targeted administration attenuated the positive association between heavy</td>
</tr>
<tr>
<td>Krystal</td>
<td>3-arm study</td>
<td>NTX vs P</td>
<td>MC R DB PC</td>
<td>AIT AD</td>
<td>12 m T 6 m PTFU</td>
<td>AA</td>
<td>Comp Cons Labs THD</td>
</tr>
<tr>
<td>2001</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe alcohol dependence.”</td>
</tr>
<tr>
<td>[56]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latt</td>
<td>2-arm study</td>
<td>NTX vs P</td>
<td>MC R DB PC</td>
<td>AD</td>
<td>12 w</td>
<td>MA AA* C*</td>
<td>Abs AE Comp Cons Cra D Labs THD</td>
</tr>
<tr>
<td>2002</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...we have shown that naltrexone with adjunctive medical advice is effective in the trea-</td>
</tr>
<tr>
<td>[126]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tment of alcohol dependence irrespective of whether it is accompanied by psychosocial in-</td>
</tr>
<tr>
<td>Monti</td>
<td>2 x 2 study</td>
<td>T1: CET + CST vs ERC then T2: NTX vs P</td>
<td>R DB PC</td>
<td>AD AAb</td>
<td>2 12 w + T1 + 12 m PT1FU</td>
<td>AA*, ERC* or CET + CST *only in T1</td>
<td>Abs Comp Cons Labs TFD THD</td>
</tr>
<tr>
<td>2001</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...results suggest the probable value of keeping alcoholics on naltrexone for longer pe-</td>
</tr>
<tr>
<td>[54]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>riods of time and importance of increasing compliance with naltrexone.”</td>
</tr>
<tr>
<td>Morris</td>
<td>2-arm study</td>
<td>NTX vs P</td>
<td>R DB PC</td>
<td>AIT AD OP</td>
<td>12 w</td>
<td>Grp. PT SS</td>
<td>Abs AE Comp Cons Labs THD</td>
</tr>
<tr>
<td>2001</td>
<td>NTX vs P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“...effective in preventing relapse to drinking in the setting of limited psychosocial trea-</td>
</tr>
<tr>
<td>[127]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tment.”</td>
</tr>
</tbody>
</table>

(continued next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration</th>
<th>Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Malley</td>
<td>4-arm study NTX vs P</td>
<td>R</td>
<td>PC</td>
<td></td>
<td></td>
<td>CS</td>
<td>T: “…superior to placebo in measure of drinking and alcohol related problems…Medication interacted with the type of psychotherapy received.”</td>
</tr>
<tr>
<td>O’Malley</td>
<td>2003</td>
<td>4-arm study NTX + PCM vs NTX + CBT then NTX + PCM vs P + PCM NTX + CBT vs P + CBT</td>
<td>R</td>
<td>PC</td>
<td>10 w</td>
<td></td>
<td>CBT PC</td>
</tr>
<tr>
<td>Oslin</td>
<td>1997</td>
<td>2-arm study NTX vs P</td>
<td>R</td>
<td>DB</td>
<td>12 w</td>
<td></td>
<td>PT</td>
</tr>
<tr>
<td>Volpicelli</td>
<td>1992</td>
<td>2-arm study NTX vs P</td>
<td>R</td>
<td>DB</td>
<td>12 w</td>
<td></td>
<td>RT Grp. ST</td>
</tr>
<tr>
<td>Volpicelli</td>
<td>1995</td>
<td>2-arm study NTX vs P</td>
<td>R</td>
<td>DB</td>
<td>12 w</td>
<td></td>
<td>Ind. PT</td>
</tr>
<tr>
<td>Volpicelli</td>
<td>1997</td>
<td>2-arm study NTX vs P</td>
<td>R</td>
<td>DB</td>
<td>12 w</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AA = Alcoholics Anonymous or other 12-step program; AAb = alcohol abuse according to DSM criteria; Abs = abstinence, % abstinence, abstinence rate, % slip into drinking, relapse, % relapse, and/or relapse rate; ACP = acamprosate; AD = alcohol dependent according to DSM criteria; AE = adverse events and/or safety measures; AIT = abstinence at initiation of treatment; C = counseling; CBT, CBT = cognitive behavioral therapy; CCS = cognitive coping skills; CET = cue exposure treatment; CM = concomitant medications; Comp = compliance, % study completion; Cons = % days abstinent, amount of alcohol consumption, days between last drink and treatment end, drinking days, drinks per drinking day, days after last relapse, heavy drinking days, pattern of alcohol use, and/or total # of drinks; Cra = craving, urge to drink, and/or alcohol related cues; CS = coping skills therapy; CSA = comorbid substance abuse; CST = communication skills training or social skills training; D = depression and/or anxiety; DB = double-blind; DD = double-dummy; ERC = education relaxation control; H = healthy; IP = inpatient; MA = medical advice; MC = multicenter; MET = motivational enhancement therapy; MM = medical management; NFZ = nefazodone; NTX = naltrexone; PC = placebo-controlled; PCM = primary care management; PD = problem drinker; PT = psychotherapy, psychoeducation, psychosocial therapy or psychosocial support; PTFU = posttreatment follow-up; QA = qualitative assessments on drinking, such as feelings or mood during drinking; R = randomized; RPP = relapse prevention therapy; REC = recidivism; RT = rehabilitation treatment program; SC = standard care; SS = social support; ST = supportive therapy; T = treatment; T1 = initial treatment; T2 = following treatment; TFD = time to first drink; THD = time to heavy drinking or time to relapse.
negative and depend on the outcome measured (Table 4). Several meta-analyses and the COMBINE study support naltrexone’s efficacy in alcohol-dependent patients [43,45,49–51]. In a meta-analysis of 24 randomized controlled trials involving 2861 patients, Srisurapanont and Jarurusaisin demonstrated naltrexone to have a favorable or significant decrease in relapse rates compared with placebo in short-term studies (≤ 12 weeks). However, analysis of medium-term (6 months) and long-term studies (1 year) demonstrated this significant effect is not maintained when naltrexone is administered over longer time periods [51]. Another meta-analysis by Bouza et al evaluated 19 randomized controlled trials involving 3205 patients also found this same effect [45].

The COMBINE study demonstrated naltrexone’s effect without behavioral counseling to be significant in decreasing the time to first drink [43]. When naltrexone was combined with cognitive behavioral therapy (CBT), patients achieved increased mean percent days abstinent, reduced drinks per drinking day, and reduced heavy drinking days per month. However, naltrexone plus cognitive behavioral therapy combined was no better than each alone in terms of primary outcomes (days abstinent and time to heavy drinking day) [43].

Several studies on naltrexone raise the issue of medication adherence as an important factor in enhancing positive outcomes [52–56]. Poor compliance could be due to the medication’s adverse effects or the patient’s decision to resume heavy drinking and cease treatment to ensure positive effects of alcohol are experienced [49,57]. However, attaining benefits from naltrexone may not only be due to the medication itself, as patients with better treatment outcomes could be more motivated toward abstinence [56].

Naltrexone hydrochloride tablets are available in 50-mg scored tablets. The recommended dosage is 50 mg per day. Peak serum concentration is reached 1 hour after dose. The most common adverse events include nausea, headache, and nervousness. Naltrexone is contraindicated in patients on opioid analgesics, dependent on opioids, or on acute withdrawal from opioids. Naltrexone is primarily metabolized by the liver and excreted in the urine, so it should be used in caution in patients with hepatic and/or renal impairment. In excessive doses (fivefold or less higher than the safe dose), naltrexone can cause hepatocellular injury.

### Naltrexone Depot Injection

Compared with oral treatment, an injectable, sustained-release naltrexone depot formulation has the advantage of preventing a patient from easily discontinuing treatment, reducing daily peak-to-trough levels, and avoiding the hepatic first pass metabolism of naltrexone [58]. The latter effect reduces levels of naltrexone’s primary metabolite 6-beta-naltrexol, which has been associated with the frequency and severity of adverse events [59].

Three different naltrexone depot formulations have been investigated to date: Vivitrol, formerly Vivitrex (Alkermes, Inc. and Cephalon, Inc.), Naltrel (Drug Abuse Sciences, Inc.), and Depotrex (Biotek, Inc.). The formulations incorporate naltrexone into injectable microspheres that facilitate the controlled release of the medication and maintenance of stable plasma concentrations over a period of several weeks [60]. The formulations differ from each other in microsphere polymer and suspension solution composition. Vivitrol was FDA-approved in the spring of 2006, the only depot formulation approved to date. It is indicated for the treatment of alcohol-dependent patients who are able to abstain from alcohol in an outpatient setting prior to treatment initiation [61].

Various products of injectable naltrexone have been studied for efficacy (Table 5). In 1 study, Garbutt administered a 380-mg dose in subjects with alcohol dependence and found that Vivitrol had a greater reduction in heavy drinking compared with placebo and a greater withdrawal rate due to adverse events compared with placebo and 190 mg–treated subjects [62]. The subset of subjects administered with the higher dose and who were abstinent during a lead-in period (abstinent 7 days prior to first dose) had greater reduction in heavy drinking days and were more likely to maintain abstinence during treatment than patients who drank during the lead-in period and those treated with placebo. There also seemed to be a gender effect, as men but not women had improved drinking outcomes among those who were administered high-dose Vivitrol. Evidence supporting the other formulations of injectable naltrexone is promising but still preliminary.

Vivitrol is supplied in single-use cartons each containing a 380-mg vial of Vivitrol microspheres, 1 vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of microspheres, 1 prepackaged syringe, 1 preparation needle, and 2 administration needles with safety device. After preparation, the suspension should be immediately administered by deep intramuscular injection. Injections should be administered every 4 weeks. Steady state is reached at the end of the dosing interval from the first injection [58,62,63]. Pain at injection site, nausea, abdominal pain, and somnolence are common adverse events, and plasma 6-beta-naltrexol concentrations are substantially lower than those seen in oral administration studies [58,62]. Serious adverse events include eosinophilic pneumonia and interstitial pneumonia [62]. Vivitrol is not metabolized by cytochrome P-450 enzymes and can be administered to patients with mild or moderate hepatic impairment.

Vivitrol is contraindicated in patients on opioid analgesics and with physiologic opioid dependence. An obvious concern for patients taking naltrexone injection or continually taking naltrexone oral tablets is interaction of opioids, either prescribed or illicitly used. Patient receiving naltrexone injection or oral naltrexone should have an abstinent-free period from opioids (eg, 7–10 days). Once on oral or injectable naltrexone,
patients may have pain or use illicit opioids. If they do, increased dosage of opioids will likely be needed to overcome the “blockage” of the naltrexone on the opioid receptor.

Should a patient have acute pain in the intervening 4 weeks after receiving an administration of naltrexone, the first options for pain management should be a nonopioid medication or a regional anesthetic. If the patient is still in pain, a general anesthetic could be used or an opioid can be used but will likely have to be administered in a higher dose and more frequently. Clinicians should be cautioned that when the injectable natrexone wears off, the frequency and dose of administered opioids should be reduced to avoid opioid overdose. For similar reasons, injectable naltrexone should be used cautiously in generally noncompliant patients who use illicit opioids. Oral naltrexone, which is approved for the treatment of opioid dependence, may be a better option.

Naltrexone depot has shown promise for a role in pharmacologic treatment of problem alcohol consumption. It is suggested that the depot formulation may be advantageous for patients with low compliance, prolonged side effects from oral naltrexone, comorbid disorders where pill management is an issue, and in settings with limited access to trained psychotherapists [49,58]. Depot formulations require provider training for proper administration to reduce local site reactions and patient refusal rate may be high from injection phobias [60].

### Naltrexone and Acamprosate Combination

Because clinical trials suggest that naltrexone may influence the positive reward pathway and acamprosate may influence the negative reward pathway, recent interest has led to the investigation of the potential of synergistic or added effects of this combination. Thus far, neither medication seems to benefit every alcohol-dependent patient, and the treatment effect size for these therapies ranges from small to medium in each clinical trial [64]. This may be due to the disposition of certain phenotypes or specific characteristics of patients that led them to preferentially benefit from a particular medication [17,65]. For example, the phenotype of a patient that chronically consumes alcohol for stimulation may benefit more from naltrexone therapy, whereas a patient who consumes alcohol to avoid the effects of withdrawal may benefit more from acamprosate therapy.

Several clinical trials have tested the efficacy, safety, and tolerability of the combined therapy in comparison...
with each therapy alone (Table 6) [43,66–68]. Kiefer et al demonstrated the combination of 50 mg/day naltrexone + 1998 mg/day acamprosate to be more effective (but not significantly so) in lowering relapse rates compared with acamprosate alone as well as increasing time to first relapse compared with acamprosate alone [67]. After patients discontinued the treatment, a 3-month open-label follow-up revealed treatment benefits among active treatments were no longer significantly different [65].

The Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study [55] was designed to evaluate naltrexone alone, acamprosate alone, and their combination, with and without behavioral therapy. In this 9-arm, placebo-controlled trial, alcohol-dependent persons ($n = 1383$) were assigned to medical management and 16 weeks of either naltrexone, acamprosate, both, or placebo, with or without a combined behavioral therapy intervention (CBI). A ninth group received CBI alone. Participants had to achieve 4 to 21 days of abstinence prior to study entry, and candidates were excluded if they had drug abuse or a psychiatric disorder requiring medication. Medical management consisted of a 9-session intervention that focused on enhancing medication adherence and abstinence using a model that could be adapted by primary care settings. The CBI consisted of up to 20 sessions of more intensive counseling delivered by alcoholism treatment specialists. The coprimary endpoints were percent days abstinent and time to first heavy drinking day. A composite secondary outcome measure, “good clinical outcome,” was also used, defined as abstinence or only moderate drinking during the last 8 weeks of the 16-week trial. Moderate drinking was defined as a maximum of 11 (women) or 14 (men) drinks per week, with no more than

### Table 6. Naltrexone and Acamprosate Combination Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Methods</th>
<th>Sample</th>
<th>Duration Care</th>
<th>Outcomes Measured</th>
<th>Investigator Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBINE 2006</td>
<td>ACP vs NTX vs ACP+NTX vs P</td>
<td>MC R DB</td>
<td>AIT AD</td>
<td>4 m T</td>
<td>AE Comp Cons Cra Labs THD</td>
<td>“No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.”</td>
</tr>
<tr>
<td></td>
<td>vs CBI only</td>
<td>PC</td>
<td>OP</td>
<td>12 m PTFU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 2003</td>
<td>4-WCS ACP-LD ± NTX-LD ± NTX-HD</td>
<td>MC R DB</td>
<td>AD OP</td>
<td>23 d</td>
<td>AE BP Labs PK</td>
<td>“Naltrexone and acamprosate, both alone and in combination at the tested doses, were behaviorally and pharmacologically safe.”</td>
</tr>
<tr>
<td></td>
<td>vs ACP-HD ± NTX-LD ± NTX-HD vs ACP-HD vs NTX-HD vs P</td>
<td>PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiefer 2003</td>
<td>4-arm study NTX vs ACP vs NTX + ACP vs P</td>
<td>R DB PC</td>
<td>AIT AD</td>
<td>12 w Grp. CBT</td>
<td>AE Cons Cra Labs TFD THD</td>
<td>“Naltrexone and acamprosate, especially in combination, considerably enhance the potential of relapse prevention.”</td>
</tr>
<tr>
<td>Mason 2002</td>
<td>3-WCS ACP + NTX-P vs ACP-P + NTX vs ACP + NTX</td>
<td>R DB H</td>
<td>7 d T</td>
<td>7 d WBT</td>
<td>AE BP PK</td>
<td>“A complete absence of negative interactions on measures of safety and cognitive function supports the absence of a contraindication to co-administration of acamprosate and naltrexone in clinical practice.”</td>
</tr>
</tbody>
</table>

Abs = abstinence, % abstinent, abstinence rate, % slip into drinking, relapse, % relapse, and/or relapse rate; ACP = acamprosate; ACP-HD = high-dose acamprosate; ACP-LD = low-dose acamprosate; AD = alcohol dependent according to DSM criteria; AE = adverse events and/or safety measures; AIT = abstinence at initiation of treatment; BP = behavioral and/or performance tests; C = counseling; CBI, CBT = cognitive behavioral therapy; Comp = compliance, % study completion; Cons = % days abstinent, amount of alcohol consumption, days between last drink and treatment end, drinking days, drinks per drinking day, days after last relapse, heavy drinking days, pattern of alcohol use, and/or total # of drinks; Cra = craving, urge to drink, and/or alcohol related cues; DB = double-blind; DD = double-dummy; H = healthy; IP = inpatient; MC = multicenter; MM = medical management; NTX = naltrexone; NTX-HD = high-dose naltrexone; NTX-LD = low-dose naltrexone; OP = outpatient; P = placebo; PC = placebo-controlled; PK = pharmacokinetics; PTFU = posttreatment follow-up; R = randomized; T = treatment; TFD = time to first drink; THD = time to heavy drinking or time to relapse; WBT = washout between treatments; WCS = #-crossover study.
2 days on which more than 3 drinks (women) or 4 drinks (men) were consumed.

Patients receiving medical management combined with naltrexone, CBI, or both had higher percent days abstinent [55]. Among patients receiving medical management with no CBI, those who received naltrexone or naltrexone with acamprosate were more likely to have a good clinical outcome (73.7% and 78.4%, respectively); the differences between these arms were not statistically significant. Acamprosate alone or in any combination with naltrexone and CBI had no effect on drinking versus placebo.

In sum, the COMBINE study failed to show a statistically significant additive effect of combining 2 naltrexone and acamprosate, for alcohol-related outcomes. Furthermore, the study demonstrated that combination therapy increases the incidence of diarrhea, nervousness, somnolence, decreased appetite, and headache compared with placebo [43,66]. COMBINE’s findings, considered in light of studies showing benefit from long-acting injectable naltrexone and a randomized trial showing no significant effect of acamprosate compared with placebo, may support naltrexone as the preferred pharmacologic intervention for alcohol dependent patients seen in general medical settings, provided appropriate algorithms are developed to guide medical caregivers [42,62]. It may be that acamprosate is most useful in patients who are undergoing withdrawal or who have significant psychiatric morbidity, 2 populations that COMBINE did not enroll.

Other combinations of pharmacotherapy, such as acamprosate or naltrexone combined with disulfiram, have had mixed results on alcohol consumption [69,70].

Choosing a Medication: Predictors of Success

The inconsistency of pharmacotherapy efficacy trials makes it difficult for physicians to easily determine if a patient will preferentially respond to one medication over another. No study to date has investigated the clinical outcomes of preferentially assigning pharmacotherapy to one group versus another based on patient characteristics. However, the preponderance of clinical studies has found that certain subgroups of patients do “better” than others on certain medications.

Patients who are older, more socially stable, and with higher motivation seem to have better treatment outcomes with disulfiram [27,32,71]. Several studies suggest patients who were alcohol-dependent earlier in life respond better to naltrexone compared with patients who had the diagnosis at an older age [72–75]. Naltrexone has also been found more beneficial in subjects with a family history of alcoholism, history of abuse of other substances, and high depression scores [74,76]. Volpicelli suggested that higher levels of anxiety, baseline craving, and somatic distress may also predict a positive treatment response to naltrexone, yet this relationship conflicts with data from other studies [76–78].

In contrast with naltrexone, there is scant evidence that acamprosate administration preferentially benefits one type of patient over another. Verhuel et al found that acamprosate was not differentially associated with family alcoholism, age of onset, anxiety symptomatology, severity of craving, or gender [24]. Kiefer et al found acamprosate treatment to be effective in alcohol-dependent subjects with low somatic distress scores, and Mason et al found acamprosate to be more effective among patients who are motivated toward abstinence [42,76].

The findings on differential relationships between patient characteristics and pharmacotherapy outcomes are not conclusive. However, the current evidence may help physicians to develop strategies when considering whether to put a patient on adjunctive medication. While there are no formal guidelines on which pharmacologic treatment to provide for specific patients, some consideration should be given to patient characteristics, including cautious use in patients with certain conditions, such as hepatic or renal disease (Figure). Further research with larger patient samples is necessary before the proposed relationships can have a significant influence in clinicians’ decision making process.

Combining Pharmacotherapy and Nonpharmacotherapy

Several nonpharmacologic therapies are worthy of mention. Behavioral therapy (CBT, CBI), motivational enhancement therapy, and 12-step program facilitation are several nonpharmacologic therapies that have shown to be effective in enhancing alcohol consumption reduction [79]. Brief interventions (mentioned earlier), motivational enhancement therapy, and medical management therapy (as described in the COMBINE study) are particularly suitable for primary care settings [43,80–83]. CBT is not a likely option, since it requires physician training and patient commitment to weekly sessions, but it can be a referral option [82]. Whitlock et al has reviewed the potential nonpharmacologic interventions, including behavioral counseling, available to primary care providers [83].

Several studies have evaluated the effects of pharmacotherapies when combined with various nonpharmacotherapies on enhancing alcohol treatment outcomes. There is strong evidence that naltrexone is more effective when combined with CBT and coping skills therapy [52,84–86]. In a trial comparing naltrexone in adjunct to CBT or motivational enhancement therapy, patients treated with the naltrexone and CBT had a significantly greater reduction in relapse rates compared with CBT alone. The naltrexone and motivational enhancement therapy patient group experienced a 13% reduction in relapse rate, but was not significantly different compared to motivational enhancement therapy only patient group [82]. In the COMBINE study, patients were treated with medical management and/or CBI.
Patients with naltrexone in adjunct to medical management fared better in regards to percent days abstinent and time to first heavy drinking day compared with the combined naltrexone, medical management, and CBI [43].

Strong evidence suggests that acamprosate is effective in adjunct to a variety of psychotherapies [87]. In the New European Alcoholism Treatment (NEAT) study, acamprosate in combination with brief intervention, relapse prevention, individual therapy, group therapy, and family therapy all yielded treatment benefit [88]. In another study, there was no significant difference in efficacy measures between acamprosate with motivational enhancement therapy (3 weekly sessions of 20 min) and acamprosate with CBT (7 weekly sessions of 60 min) [89]. Furthermore, in Hammarberg et al, acamprosate in adjunct to different intensities of psychosocial interventions (4 sessions with a psychiatrist within 6 months versus 4 sessions with a psychiatrist + 10–15 sessions with a psychiatric nurse within 6 months) yielded no significant difference in efficacy [90]. In the COMBINE study, efficacy outcomes were not significantly different between acamprosate and medical management and acamprosate and CBI [43].

**Pharmacotherapy and Psychiatric Comorbidity**

Patient selection in the majority of studies on AUD pharmacotherapy has generally excluded patients with severe psychiatric disorders and substance abuse disorders. The lack of studies involving subjects with comorbid psychiatric problems may be attributable to many factors, such as the desire to simplify study design, involve less intensive patient management, and decrease expense [91].

However, the Epidemiologic Catchment Area (ECA) Study and National Comorbidity Study (NCS) have demonstrated that comorbidity is a common problem among patients with...
ALCOHOL USE DISORDERS

alcohol problems [73,92,93]. In the ECA study, 45% of individuals with an alcohol use disorder had a psychiatric or other substance use disorder [92]. Individuals with schizophrenia, bipolar disorder, anxiety disorders, and antisocial personality disorder have the highest rates of AUDs. Anxiety and mood disorders are the most common comorbid disorders among women with a history of alcohol abuse or dependence, while drug use disorders and antisocial personality disorder are the most common among men [73].

Among the FDA-approved medications, only naltrexone and disulfiram have been studied in AUD patients with any psychiatric comorbidities. In a 12-week study of 254 patients with an Axis I psychiatric disorder and alcohol dependence, the naltrexone and disulfiram treatment groups were significantly more efficacious compared with placebo in decreasing drinking days per week and increasing consecutive days of abstinence. Furthermore, the combination of the 2 medications was no more beneficial than naltrexone and disulfiram alone [70]. Several studies have supported the safety of naltrexone and disulfiram in AUD patients with comorbid psychiatric disorders with monitoring [70,94–98]. Studies have also suggested an association between disulfiram and a reduction in alcohol and cocaine use [99–101]. There is some evidence that the use of serotonin reuptake inhibitors for depression reduces alcohol consumption and major depression disorder symptoms [102]. In addition, there is some evidence that serotonin reuptake inhibitors reduce alcohol consumption in patients who are not depressed [103]. Further research regarding antidepressant treatments for alcohol-dependent individuals is warranted.

Despite the very limited evidence supporting the use of pharmacotherapies in AUD patients with psychiatric comorbidities, effective treatment for this patient population is imperative. Problem alcohol drinkers with psychiatric comorbidities have more hospital admissions, poorer treatment outcomes, and an increased risk of suicide compared with problem drinkers without psychiatric diagnoses [73,104–106]. Also, it has been suggested that these patients are more reluctant to participate in self-help groups and have a decreased motivation and ability to learn new psychosocial treatments compared with those without psychiatric disorders. Thus, adjunct pharmacologic treatment may be more necessary in this patient population [102]. Although further evidence has yet to be gathered, there is potential to treat this population in primary care settings with AUD pharmacotherapy.

Summary and Recommendations

We examined the evidence for pharmacotherapy for problem alcohol consumption that can be used in primary care settings. Biological and phenotypic models provide rationale for the primary care provider in promoting pharmacologic treatment in primary care settings. The available research has shown that disulfiram, naltrexone, and acamprosate are effective for treating patients with alcohol problems. Certain patient characteristics promote enhanced outcomes for each medication. Whether combinations of pharmacotherapies or combinations of pharmacotherapy with nonpharmacotherapy enhance outcomes for problem drinkers are active research topics.

It is important for clinicians to realize that there is no “home run” treatment for alcohol problems. Certain medications may be favorable considering certain patient characteristics or treatment goals. Caution should be used in treating certain patient populations, such as those with liver disease (eg, disulfiram, naltrexone), renal disease (eg, acamprosate), or those in need of opioid analgesia (eg, naltrexone). Naltrexone or acamprosate may be more appropriate for the patient who seeks alcohol consumption reduction (but not elimination), while disulfiram may be more appropriate for supervised, abstinence-goal treatment environment. Furthermore, a 4-week depot injection of naltrexone may be superior to oral naltrexone, acamprosate, and disulfiram when considering a patient with known medication noncompliance.

Just as in using pharmacotherapy for other medical and behavioral health conditions, if nonresponse occurs, the clinician should consider switching to another agent. If nonpharmaceutical and/or pharmaceutical interventions are not working for a patient in the primary care setting, the provider should consider referral to an addiction specialist or comprehensive treatment program. Regardless of the treatment chosen, the clinician should consider alcohol consumption as a chronic medical disorder, which waxes and wanes in intensity and harm, and consider the impact of this condition on the patient’s overall environment. Clinicians should examine the gamut of medical, social, and environmental consequences of alcohol consumption and attend to these consequences as ongoing pharmaceutical and nonpharmaceutical alcohol treatment is underway.

Corresponding author: Adam J. Gordon, MD, MPH, Center for Health Equity Research and Promotion, Mail code 151-C: CHERP, University Drive C, Pittsburgh, PA 15240, adam.gordon@va.gov.

Funding/support: This work was funded by the Reynolds Fellowship in Clinical Research Training in Adult Psychiatry (NIMH: MH016804). Dr. Gordon has received support for this work by the VISN 4 MIRECC, AA13566-01 NIAAA, and a VA Health Services Research & Development Career Development Award (RCD-0038-2).

Financial disclosures: None.

Author contributions: conception and design, SP, AG; drafting of the article, SP; critical revision of the article, AG.

References

1. Grant BF, Dawson DA, Stinson FS, et al. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence:


23. Kumari M, Ticku MK. Regulation of NMDA receptors by ethanol. Prog Drug Res 2000;54:152–89.


35:176–87.
64. Johnson BA, Ait-Daoud N. Neuropsychopharmacological treatments for alcoholism: scientific basis and clinical findings. Psychopharmacology (Berl) 2000;149:327–44.


